Department of Agriculture

Office of Agricultural Biotechnology

# Minutes

## Agricultural Biotechnology Research Advisory Committee

December 16-17, 1993

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**U.S. DEPARTMENT OF AGRICULTURE**
**AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE**
Minutes of Meeting
December 16-17, 1993

## Time, Place, and Participants

The U.S. Department of Agriculture (USDA) Agricultural Biotechnology Research Advisory Committee (ABRAC) met December 16 and 17, 1993, in the Ballston Room of the Holiday Inn Ballston, Arlington, VA. The meeting had been announced in the *Federal Register* and was open to the public.

Members present included:

David Kline, Chair, State University of New York, New Paltz, NY;
Anne Vidaver, Vice Chair, University of Nebraska, Lincoln, NE;
William Witt, Food and Drug Administration, National Center for Toxicological Research, Jefferson, AR;
David Andow, University of Minnesota, St. Paul, MN;
Stanley Pierce, Rivkin, Radler & Kremer, Uniondale, NY;
Walter Hill, Tuskegee University, Tuskegee, AL;
Anne Kapuscinski, University of Minnesota, St. Paul, MN;
Susan Harlander, Land O'Lakes, Inc., Minneapolis, MN;
James Lauderdale, Upjohn Company, Kalamazoo, MI;
Pamela Marrone, Novo Nordisk Entotech, Inc., Davis, CA;
Deborah Letourneau, University of California, Davis, CA;
Rudy Wodzinski, University of Central Florida, Orlando, FL;
Ronald Sederoff, North Carolina State University, Raleigh, NC;
Alvin Young, Executive Secretary, ABRAC, and Director, USDA Office of Biotechnology, Washington, DC.

USDA Office of Agricultural Biotechnology (OAB) staff present included Daniel Jones, Maryln Cordle, Martha Steinbock, Marti Asner, Chuck Lewis, and Barry Stone. Others present are listed in Appendix A.

## December 16, 1993

### Call to Order and Introductory Remarks

Dr. Kline called the meeting to order at 9:05 a.m. After the ABRAC members and meeting guests introduced themselves. He asked the ABRAC to approve the agenda. The agenda was approved.

Dr. Young reported that the new charter for the ABRAC was awaiting approval by the Secretary of Agriculture. He pointed out that, unlike many other Federal advisory committees, the ABRAC has been rechartered and funded for fiscal year 1994. He also noted that four members of the ABRAC will need to be replaced.

Dr. Young also reported that a scheduled discussion of organic food and biotechnology had been withdrawn at the request of the National Organic Standards Board. The Board wanted more time to decide what issues it wants the ABRAC to consider. Dr. Young said he hoped the discussion could be rescheduled for a future ABRAC meeting.

Dr. Kline introduced Dr. Kapuscinski, who reported on the Workshop on Performance Standards for Aquatic Research.

**Workshop on Performance Standards on Aquatic Research**

Dr. Kapuscinski said the workshop, which took place from August 18 through 20, 1993, in Minneapolis, drew 98 participants from all over the United States and some foreign countries. Participants came from industry, academia, government, and non-government organizations and represented many scientific disciplines.

The workshop opened with a plenary session that included an introduction and an outline of the draft performance standards. Three breakout groups met for the rest of the first day and all of the second day; each group studied a different section of the draft. The third day consisted of another plenary session in which the groups presented their comments on their assigned section of the draft. Participants agreed that the effort to develop such standards was important and timely.

The standards are designed to provide scientists with guidelines for assessing and managing the ecological safety of experiments involving genetically modified fish and shellfish. The standards take into account the need for sufficient information, the characteristics of both the parental and modified organism, the scale of the potential release of modified organisms, the modified organism's dispersal abilities, and the organism's interaction and effects on ecosystem structure and function.

Part IA of the standards is designed to identify those genetically modified organisms that can be excluded immediately from the standards. Part IB guides the researcher in characterization of the genetically modified organism. Part IC addresses the need to characterize the ecosystem into which the modified organism would be released. Integration of these parts is depicted in the flow charts that follow.

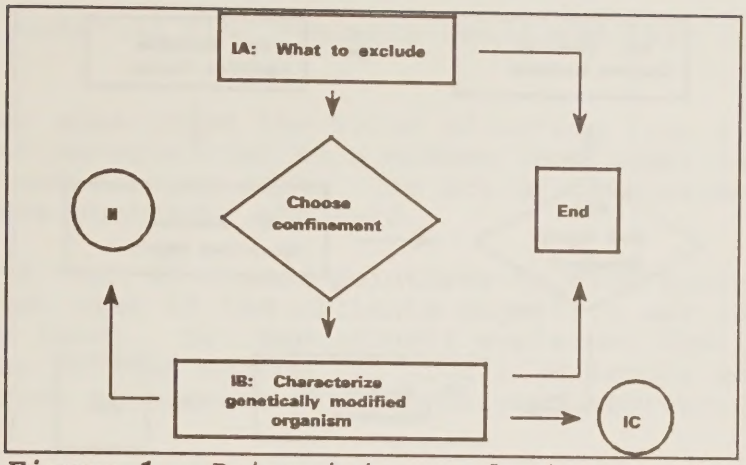


*Figure 1: Determining exclusions, and characterizing the modified organism*

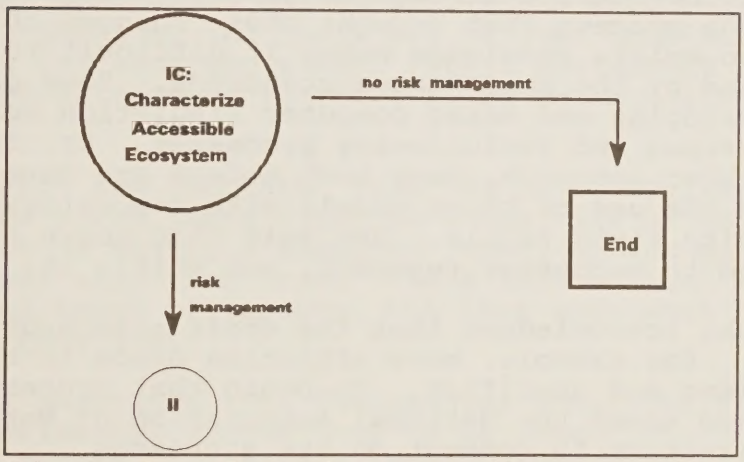


*Figure 2: Characterizing the accessible ecosystems*

Dr. Kapuscinski said that the workshop participants believed that the August 4, 1993 draft standards were too vague in specifying how much risk management is needed. They suggested rearranging the questions and answers in the standards so that researchers could conclude that risk levels were low, medium, or high.

The next part of the standards, Section II, addresses actual management of risk in experiments involving genetically modified fish and shellfish. Risk management would be designed to achieve a negligible amount of release from such an experiment, and management recommendations should correspond to the level of risk (low, medium, or high) involved. The flow chart that follows depicts how the performance standards would address risk management.

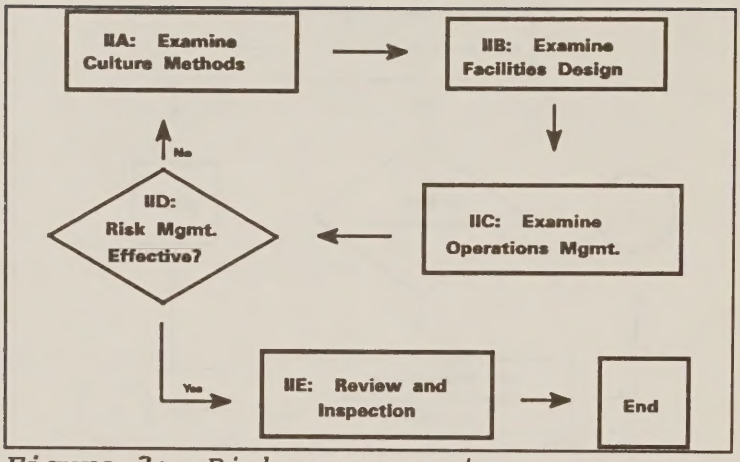


*Figure 3: Risk management*

Dr. Kapuscinski said the workshop participants were most concerned with deliberate structural genetic changes in the genome, not the process that brought those changes about. She noted that incomplete knowledge makes it difficult to answer the questions posed by the performance standards. Some participants suggested developing and using computer simulation models of aquatic ecosystems and evolutionary processes. Dr. Kapuscinski believed the best approach, once such models are developed, would be to combine the use of those models with laboratory experiments and, later, with field trials. She said that above all, the standards need to encourage research, not stifle it.

Dr. Kapuscinski acknowledged that the draft standards have some shortcomings. For example, more attention needs to be paid to marine organisms and shellfish. To begin that process, Dr. Kapuscinski had asked the National Association of Marine Laboratory Directors to comment on the standards.

Dr. Kapuscinski said the next step is to revise the draft standards, and that several members of the ABRAC aquatic working group are doing that. Revisions are to be sent to Dr. Kapuscinski in mid-January; the next draft will be sent for another round of comment to ABRAC members, workshop participants, and anyone else who is interested.

Dr. Kapuscinski asked ABRAC for its views on having three risk levels: high, medium and low. Dr. Kline asked Dr. Kapuscinski to define medium risk. Dr. Kapuscinski said that a medium level of risk might indicate that it is reasonably likely that enough modified fish could escape to establish a new population. In contrast, a high risk might mean that such an escape is almost guaranteed, and that the modified trait would have a significant impact on the environment. Another definition of medium risk would be that an escaped modified fish could survive and reproduce in the wild. A low level of risk would indicate that

any escaping modified fish probably would not live long enough to reproduce.

Dr. Letourneau questioned the value of moving from a scheme that identifies and manages risk to a scheme that identifies, categorizes, and manages risk. The act of categorization makes the scheme more abstract, she said.

Dr. Kline said that it seemed pointless to distinguish between medium and high risk if the ultimate objective was to bring risk down to a low level. Dr. Kapuscinski explained that distinguishing between medium and high risk levels would help ensure that risk management procedures were appropriate and not excessive.

Dr. Andow pointed out that the three levels of risk agreed upon at the workshop may have resulted from an unwillingness by participants to say their experiments carried no risk at all. He suggested that some risks can be eliminated from consideration for certain organisms, and there may be some problems with attempting to fit each experiment into a particular category of degree of risk as opposed to identifying and managing specific risks.

Dr. Pierce asked how the term "risk" is being applied within the standards. He noted there might be a low risk of escape but a very high risk of having a damaging impact on the environment. Dr. Kapuscinski said that "risk" takes into account scale of the experiment and types of impacts, but that more work needs to be done on this question.

Dr. Wodzinski suggested that fundamental questions about the proposed experimental system need to be asked before the modification begins. If safety is an issue, he said, it might be a good idea to ask whether the experiment should be conducted in the first place.

Dr. Vidaver asked why the *Guidelines for Research Involving Planned Introduction into the Environment of Genetically Modified Organisms* (hereafter referred to as the Guidelines) were not used to help deal with these questions. Dr. Kapuscinski said the working group began by using the Guidelines as a template, but found that they were too sketchy to provide the depth of information that we felt was appropriate for the performance standards. Fish and shellfish differ significantly from most terrestrial organisms used in agriculture in that they are not very far removed from the wild and there is often a high level of hybridization across species and even across genera.

Dr. Eric Hallerman, a member of the ABRAC Working Group, noted that the Guidelines were used in developing some of the questions and in defining many terms. Although we didn't use the format of

addressing the parental organism first and then the modified organism, the basic concepts were retained in the performance standards.

Dr. Kline then introduced Ms. Cordle, who discussed the scope of the Performance Standards.

## Scope of the Performance Standards

Ms. Cordle said that the aquatic workshop participants found shortcomings in the definition of "scope" in the August 4, 1993 draft of the performance standards. That draft defined scope as follows:

> *The performance standards address the ecological safety of research involving freshwater and marine fish, crustaceans, and mollusks, with particular emphasis on organisms expressing novel hereditary traits or traits under novel regulatory control, independent of the technology used for genetic modification.*

The workshop participants recommended that the definition be modified in the following four ways:

- The scope of organisms covered by the standards should be based on deliberate structural changes in the genome, not on the more ambiguous concept of novel traits.
- Exclusions should be clearly specified at the very beginning of the definition.
- Traditional breeding that results solely in changes in allele frequencies in the population should be excluded.
- Interspecific hybrids that commonly occur in the accessible environment should be excluded.

The participants said the new standards should contain clear objective criteria; should be practical to apply; and should focus on deliberate, structural genetic changes. Moreover, the standards should not cover all introductions of fish and shellfish, and they should avoid duplication of existing guidelines. For example, current regulations already cover exotic and noxious fish species.

Based on discussions at the workshop, the proposed new definition is as follows:

> *A. Except as listed in B. below, the standards apply to freshwater and marine finfish, crustaceans, and mollusks whose genomic structure has been deliberately*

*modified by human intervention. Examples of deliberately induced changes in genomic structure include:*

- *additions or substitutions of genetic material[1] derived from a taxonomically distinct species or subspecies;*
- *alterations of genetic material occurring within the genome;*
- *artificially induced rearrangements (e.g. translocations, inversions);*
- *chimeric organisms generated from fusion of embryos from taxonomically distinct species or subspecies.*

*B. The standards do not apply to organisms whose genomic structure has been modified by humans solely by the following means:*

- *intraspecific artificial selection/breeding by natural reproductive processes or intraspecific captive breeding, including use of artificial insemination, embryo splitting, or cloning;*
- *interspecific hybridization provided that (i) the hybrid occurs naturally or has been extensively introduced (e.g., through stocking) in the environment accessible to organisms escaping from the research site or in a similar environment, and (ii) there are no indications of adverse ecological effects for the specific hybrid in question.*

Under the discussion of rationale, Ms. Cordle said that the top of page 4 of Attachment A in Handout #201 (attached as Appendix B) should be changed to read as follows:

*The process of chromosomal manipulation may yield a mosaic individual in which some but not all cells, possibly even germline cells, contain different paternal chromosome fragments. This can occur, for example, when irradiated sperm from the same or different species is used for chromosome-mediated gene transfer and the resulting fertilized eggs are then manipulated experimentally to yield gynogenetic*

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[1] *Genetic material includes chromosomes, chromosomal fragments, mitochondrial DNA, genes, transposable elements, non-coding DNA (including regulatory sequences), and synthetic DNA sequences.*

*diploids (Thorgaard, et al, 1985; Disney, et al, 1987). This makes it hard to predict the genotype and phenotype of descendants.*

Ms. Cordle said that she hoped the ABRAC would address the following questions with respect to the scope of the performance standards:

1. Should the scope definition be based on human-induced structural change to the genome?

2. Do the examples of structural changes clearly indicate the human-induced changes of interest? What changes, if any, should be made to the definition and examples, and why?

3. Does the ABRAC agree with the proposed exemption for interspecific hybrids?

4. Is there scientific evidence on which to base exemption of certain chromosomal-set manipulated organisms?

5. Should targeted genetic rearrangements be included? Based on science, is the rationale provided a reasonable one?

6. Are there specific questions that should be posed to the ABRAC Working Group on Aquatic Biotechnology and Environmental Safety to investigate further on the scop issue before revised standards are sent to the workshop participants and others for another round of comments?

Dr. Marrone questioned the focus on genotype as opposed to phenotype and claimed it was a dangerous precedent. She said that by making such a distinction, the definition focuses on the process by which a product is made, not the product itself. Ms. Cordle explained that the workshop participants were concerned with preserving the integrity of the gene pool.

Dr. Kapuscinski said that structural genetic changes are the ones that are most likely to affect the evolutionary potential and adaptation of natural populations. She explained that changing the genome was a clear criterion by which the workshop participants could decide what the performance standards would and would not cover. When you begin using the performance standards, you then look at whether the structural genetic change results in a phenotype of concern. Just because your project falls under the scope of the standards doesn't mean that restrictions on your experiment will be needed.

Dr. Wodzinski said that finding structural changes in modified organisms simply was not practical. It would require sequencing all the nucleic acids to see if a structural change occurred. Dr. Kapuscinski explained that a researcher who suspects a

structural change has occurred (because of deliberate modifications attempted as part of the research) would determine if such a change posed any kind of risk. Not every change would pose a risk, she added.

Dr. Sederoff said that spontaneous changes, or those changes that are equivalent to spontaneous, should be specifically excluded from the standards.

Dr. Andow said that even though some believe that traditional breeding practices are poorly regulated, the scope definition apparently attempts to exclude such practices. He asked why traditional practices should be left out. Dr. Kapuscinski said that the impacts of traditional breeding are being addressed by state agencies and the American Fisheries Society, citing a major conference scheduled for March 1994. Dr. Wodzinski said there is a precedent to exclude traditional breeding in plant biotechnology, and he agreed with excluding traditional breeding of fish and shellfish.

Dr. Meryl Broussard, Cooperative State Research Service, said at the workshop they considered the question of whether traditional selective breeding results in a novel value of a quantitative trait. He asked what constitutes a "novel quantitative trait?" Dr. Sederoff pointed out an internal contradiction in the term "novel quantitative." He said that if it is not qualitatively different, it is not novel.

Dr. Kapuscinski said "quantitative trait" refers to one controlled by more than one gene. Dr. Sederoff asked how large a quantitative difference needs to become before it is regarded as qualitative. Dr. Andow said this kind of uncertainty is a problem with regulating solely on the basis of phenotype. Dr. Sederoff argued that significant quantitative changes can be controlled by genes that are qualitative in their effects, and he suggested that the operative term should be "qualitative."

Ms. Cordle referred to the rationale for exempting traditional breeding on p. 4 of Exhibit 201 (attached as Appendix B). [Staff note: This explanation did not use quantitative/qualitative terminology, but focused instead on the likelihood of novel unfamiliar traits arising from differing allele frequency distributions, and the relative risk involved in inadvertent escape from research and development, compared with introductions involving fisheries stocking programs and commercial aquaculture.]

Dr. Althaea Langston, Animal and Plant Health Inspection Service, said that the scope definition oversteps the bounds of the ABRAC. The ABRAC was established to deal with agricultural biotechnology as defined by the Coordinated Framework of 1986. The definition of genetically engineered or genetically modified organisms

should exclude traditional breeding, cross breeding, artificial insemination and hybridization which can occur naturally, or by the simple addition or mixing of gametes from different individuals or species. The scope should deal with modern biotechnology only, she concluded.

Dr. Kapuscinski replied that ABRAC had consistently adhered to a product-based focus rather than process-based, as Dr. Langston seemed to imply was more appropriate. Dr. Kapuscinski noted that the proposed definition does exempt traditional selective breeding.

In response to Dr. Kapuscinski's question on what Dr. Langston thought should be included under the standards, Dr. Langston said the standards should address manipulations of the genome that could not occur naturally. Dr. Kapuscinski pointed out that pressure and heat shocks and even irradiated sperm are used to produce triploids. Dr. Langston contended that such organisms are not under the Coordinated Framework or within the definition of modern biotechnology. She said triploids should be excluded. Dr. Kapuscinski disagreed, pointing out that ploidy-manipulation can have as dramatic a change in phenotype as is caused by gene transfer.

Drs. Letourneau and Sederoff contend that the ABRAC's purview is not limited to recombinant DNA alone, and that such a limitation would be difficult to defend scientifically. Dr. Andow said that one of the contradictions in the Coordinated Framework is that some things are defined on the basis of process, but we're asked to ignore that. Dr. Young said that the mandate of the Biotechnology Advisory Committee doesn't say our recommendations should be confined to "process;" it is important for considerations to be based on science. Committee members have had experience in so many areas of science that you can bring some perspective into the new technologies, and some of those perspectives are from the old technologies.

Dr. Sederoff suggested a change, in page three of Attachment A, under the rational for including artificially induced rearrangements within the scope. He suggested revising the second sentence in that section that now reads, "They involve no new genetic material; most natural mutations, although not all, are deleterious and reduce the organism's fitness." The revised sentence is, "They involve no new genetic material although natural mutations can be deleterious and reduce the organism's fitness." Dr. Sederoff contends that most mutations are neutral. Dr. Andow asked whether most translocations and inversions are neutral? Dr. Sederoff said he believes they are, pointing out that the DNA in most animals and plants has no known function, and so rearrangements and mutations of all kinds that occur in those sequences are not detected and have no effect on phenotype.

Dr. Vidaver said, based on the discussion, there's an argument for focusing on phenotype, and not the genotype. She pointed out that a lot of previous work addressed defining scope principles for biotechnology, and raised caution and concern about resurrecting the arguments. Dr. Kapuscinski said her concern with that approach was that each researcher would have to go at least part way into Section I to answer questions about the phenotype of their particular organism before they would be excluded.

Dr. Kapuscinski said that if the ABRAC insisted that the scope document apply to phenotypes instead of genotypes, the participants at the workshop would be extremely upset. Dr. Hallerman said that a genotypic definition of scope permits more clarity than a phenotypic definition would. Ms. Cordle asked how one might construct a phenotypic definition without triggering a risk assessment.

Dr. Wodzinski suggested that the specifications of what is excluded should be phenotypic, and begin with the following: "Because of past practices, the following are excluded." Dr. Kapuscinski said she could not defend that proposal scientifically, and pointed out that some ploidy manipulations cause problems, while others do not.

Mr. Charles Brown, Animal and Plant Health Inspection Service, who attended the Workshop, said the participants tried to develop a scientific document irrespective of things that happened in the past. They agreed you should start with genotype and then move forward from there in applying the standards and identifying low risk organisms that could be exempt early on in the standards. Mr. Chris Mann, a Congressional staff member, suggested that the views of the regulated community be considered, and recommended that the ABRAC not base current decisions on those made in 1986, when the Coordinated Framework was adopted.

Another guest, Dr. Louis Pribyl, noted that this discussion was similar to a debate that occurred when the U.S. Food and Drug Administration (FDA) created a document on biotechnology in foods two years earlier. He suggested that the food document be used as a model for the aquatic performance standards, and added that those who are being regulated need to know right away what is being excluded.

Ms. Cordle pointed out a significant difference. The scope for the standards tells a researcher if he or she should address certain questions before beginning an experiment. There is no regulatory application or third party official involved in that decision. Dr. Vidaver said the matter warrants discussion and care simply because, while not obligatory at this point, the standards could become a regulatory document de facto.

Dr. Kline said that even though the ABRAC needed to agree on a definition of scope, it might not be possible to achieve such agreement at the current meeting.

After a lunch break and consultation with Dr. Kline, Drs. Kapuscinski and Hallerman indicated that they wanted to complete the revision of the entire performance standards and present the revised draft to the ABRAC at its May, 1994 meeting. At that time, the issue of scope could be reconsidered. In the meantime, those who oppose the currently proposed definition of scope were encouraged to submit written comments. The May draft will indicate which areas might change if the definition of scope changed.

Dr. Kline then introduced Dr. Ann Lichens-Park of the National Biotechnology Impact Assessment Program (NBIAP).

**Update on Biotechnology Risk Assessment Research**

Dr. Lichens-Park said that the administrative provisions and request for applications for NBIAP grants were being finalized and would be published in the *Federal Register* within a month. She said there were three categories of proposals:

- Developing new risk assessment methods and procedures;
- Creating information systems and computer decision models; and
- Developing risk assessments of environmental fate as correlated with facts.

Dr. Lichens-Park said that while NBIAP valued the ABRAC's advice in developing the request for proposals, there was concern that because ABRAC members also can apply for grants a conflict of interest could result. Moreover, because the ABRAC could provide such advice at its meetings, ABRAC members might have a head start and an unfair advantage over other potential grant applicants.

Dr. Pierce said that ABRAC members must excuse themselves from applying for NBIAP grants. After some debate, the rest of the ABRAC agreed that when it does provide advice on NBIAP solicitations, ABRAC members should not apply for NBIAP grants. However, several ABRAC members expressed dissatisfaction over not having been consulted on the current round of requests for grant proposals. They pointed out that it was unfair for ABRAC members to be unable to apply for grants when they had not had the opportunity to provide advice to NBIAP. Moreover, the ABRAC wants to provide such advice.

Dr. Young suggested that ABRAC meetings be scheduled so that they could provide timely advice to the NBIAP about its solicitation. Dr. Lichens-Park said that the ABRAC's scheduled May, 1994, meeting would be a good opportunity to provide advice for the solicitation that would be issued in the fall of 1994.

The ABRAC members agreed that discussing the grants at its meetings did not pose a problem. They noted that its recommendations generally are very broad, and that the NBIAP is free to reject any suggestions. Moreover, ABRAC's meetings are open to the public and are announced beforehand.

Dr. Kline thanked Dr. Lichens-Park, and introduced Ms. Karen Rogers of KKR & Company, who discussed issues in biotechnology education.

**Issues in Biotechnology Education**

Ms. Rogers said that biotechnology has been a tough sell to the public since its beginnings, and presented some statistical information on why educating the public on biotechnology has been a problem.

Two surveys—one from the Congressional Office of Technology Assessment (OTA) in 1987 and one from Hoban in 1990—indicate that even though many biotechnology advances come from private industry, the public does not have much confidence in industry spokespersons. Of those surveyed, 86 percent found university scientists to be the most credible, followed by manufacturers (45 percent) and the news media (43 percent). Another problem facing biotechnology advocates, she said, is that until recently no products resulting from biotechnology were commercially available.

Ms. Rogers cited a 1987 paper by Sandman suggesting that people tend to accept new technology if individuals control that acceptance, acceptance is voluntary, the risks are known, the products are familiar, and the process is perceived as being socioeconomically fair.

Ms. Rogers said these polls and surveys indicate that public and consumer education about biotechnology should have begun 10 years ago, and that the campaign should have been led by university scientists. The cumulative effect of telling the same story over and over would have resulted in greater public acceptance of biotechnology.

Instead, Hoban's survey indicates that by 1990, 29 percent of the population felt that biotechnology does more harm than good—up from 16 percent in the early 1980's. The OTA survey showed that while 92 percent of the population thinks solar energy will make

lives better, only 66 percent thinks biotechnology will benefit our lives.

Future efforts to promote biotechnology should recognize that in a 1992 consumer survey, respondents said that lower prices are more important than food quality when choosing food, and that biotechnology is more acceptable when applied to plants than to animals. Consumers also consider labeling for pesticides and irradiation more important than for biotechnology. Women are less accepting of biotechnology than are men. Religious, health, and environmental concerns all play a role in consumer opinions about biotechnology.

Ms. Rogers said that negative developments about biotechnology generate far more news coverage than positive developments do. As an example, she cited an ordinance passed by the Chicago city council that would have required labels for biotechnology products. Passage of the ordinance, which was aimed at Calgene's new tomato, generated considerable media coverage. However, when the city council realized how many products would have to be labeled, they repealed the ordinance. The repeal drew no publicity at all.

Ms. Rogers predicted that biotechnology issues will become as important to the public as other dietary issues are, and that the labeling of products as biotechnology-free will occur very soon.

Public education is critical to acceptance of biotechnology. Ms. Rogers noted that most people care about science and technology and believe that it improves our lives. Moreover, most people want to know more about biotechnology—and if they don't know enough about it, they will resist it.

The National Agricultural Library has found that 75 biotechnology education programs are being conducted in 39 states. Among the notable programs are conducted by the St. Louis Math and Science Centers, the National Future Farmers of America (FFA) Foundation, American Cyanamid, Biotechnology Industry Organization, the University of Wisconsin Biotechnology Center, the University of Maryland, and the Pennsylvania Biotechnology Association. Most of these programs are formal and are part of the curricula of the public schools.

Ms. Rogers said that little is being done to reach today's consumers. However, any such efforts need to realize that:

- Today's consumers have less faith in science than they once did.

- Critics of biotechnology use sensationalism to get their points across.

- Advances in biotechnology come mainly from industry—and industry is not trusted.

- Regulatory control over communications, particularly with respect to false claims, have made biotechnology education difficult. This is because until a product actually hits the market, regulators watch for material that could be considered a false claim—and until recently, no products from biotechnology have been available on the commercial market.

- This regulatory control has given critics of biotechnology an 11-year head start over supporters.

- It is important to differentiate between emotion and fact when discussing biotechnology.

- Discussions of biotechnology need to focus on both long-term and short-term considerations.

Ms. Rogers suggested that educational efforts involving biotechnology shift their focus from the technology itself to the positive effects such technology could have. Biotechnology could help improve human health, the environment, the economic status of the developing world, and human nutrition. By dealing with these concerns, and giving the pro-biotechnology campaign an issues-oriented tilt, more favorable publicity of biotechnology could be generated. However, such discussions also need to deal honestly with any risks biotechnology may pose.

Ms. Rogers suggested that the ABRAC consider the following questions:

1. Who should communicate with the public on biotechnology products and issues?

2. Who should pay for the new communications strategy?

3. Is the issues approach viable?

4. How should unacceptable applications of biotechnology be dealt with?

5. What should be the components of an issues-based biotechnology education plan?

6. Is a credible, central information clearinghouse needed?

Dr. Hill asked if the movie *Jurassic Park* had had a negative effect on public perceptions of biotechnology. Ms. Rogers said the public appears to have viewed the movie as a dinosaur epic, not as an indictment of biotechnology.

Ms. Rogers said that one way to make the acceptance of biotechnology appear more voluntary is to add a consumer representative to the ABRAC. Dr. Young noted that USDA already has a Consumer Advisor who deals with consumer concerns.

Ms. Rogers also said that when people are under stress or feel coerced, they do not think objectively. Consequently, efforts to educate the public about biotechnology must be pro-active. People who know the most about biotechnology have the most positive views of it. Dr. Jim Rasekh, Food Safety and Inspection Service, noted that the public's perception of food is different from its perception of other products.

Dr. Lauderdale asked if an educational program can be implemented independently from other products. Ms. Rogers said that such independence is essential. Companies need to prepare the way, but the mechanism to deal with global issues needs to be developed.

Dr. Harlander noted that as an employee of an agricultural cooperative (Land O'Lakes), she has had a chance to see some of the powerful ways that people can be involved in product development. Land O'Lakes utilizes its farmer members and consumer advisory panels in ways that increase understanding and influence product direction.

Dr. Young recalled that a recent book on biotechnology published in the Netherlands suggested that people simply want to know if their food is safe.

Dr. Robert Zimbelman, a guest, said that the playing field in biotechnology is uneven. Those who claim biotechnology is unsafe do not need to document their claims; however, those who claim such products are safe must back up those claims. The question he posed is do people want to know, or do they want to trust.

Dr. Letourneau warned that any educational efforts cannot force people to accept biotechnology. Educational programs can only present people with the facts upon which they will base their own conclusions.

Mr. David Holzman, a reporter with *BioWorld*, said that any biotechnology educational programs must be scrupulously honest. For example, biotechnology could benefit sustainable agriculture, but it also could cause harm. He said that bovine somatotropin was the wrong product to start with. Ms. Kelly Day, Economic Research Service, agreed, and pointed out that because milk is an animal product and is fed to infants, any efforts to change it (particularly by adding a hormone) would cause profound uneasiness among consumers.

Dr. Andow suggested that efforts to determine the safety of products derived from biotechnology come from USDA. The Department is better positioned than private companies to determine the safety of such products.

Dr. Kline thanked Ms. Rogers, and asked Dr. Young to discuss the Federal Biotechnology Research Crosscut.

**Federal Biotechnology Research Crosscut**

Dr. Young said that on November 23, 1993, President Bill Clinton issued an Executive Order that established a Presidential Committee of Advisors on Science and Technology. The 15-member committee includes representatives from industry, academia, research institutions, NGO's, and others.

The Executive Order also establishes a new National Science and Technology Council. This new body merges the Federal Coordinating Council for Science, Engineering and Technology (FCCSET), the National Space Council, and the National Critical Materials Council. The members of the new council include representatives from the Departments of Defense, Energy, Health and Human Services (HHS), State, and Interior; the National Aeronautics and Space Administration (NASA); National Science Foundation (NSF), Office of Management and Budget (OMB); Environmental Protection Agency (EPA); the White House Office of Science and Technology Policy (OSTP); and the National Security Agency (NSA). Although USDA currently does not have a representative on the Council, Department officials have asked that that decision be reconsidered.

Under the old FCCSET structure, there was no way to implement recommendations, and no capability to make policy statements. In contrast, the Council can set science and technology policy, because the members have Cabinet status. The Council will ensure that national science and technology policy is coordinated and consistent, and integrated throughout the Federal government.

The Council includes several coordinating committees:

- Health, Safety and Food Research and Development (to be co-chaired by HHS and USDA;
- Fundamental Science and Engineering Research and Development (under which is a Biotechnology Research Subcommittee);
- Information and Communications;
- Environment and Natural Resources;
- Civilian Industrial Technology;

- Education and Training;
- Transportation;
- National Security, and
- International Science, Engineering, and Technology.

Staff work for the coordinating committees will be directed by an Associate Director in OSTP. These include an Associate Director for Science, an Associate Director for Technology; and an Associate Director for the Environment.

Dr. Young then presented Dr. Tom Brady of the National Science Foundation, who discussed the work of the Biotechnology Research Subcommittee.

**Biotechnology Research Subcommittee**

Dr. Brady noted that Neal Lane of the NSF and Dr. Harold Varmus of the National Institutes of Health chair the Biotechnology Research Subcommittee's parent committee, the Fundamental Science and Engineering Research and Development Committee.

Among the Federal agencies involved in biotechnology research are the Agency for International Development (AID), HHS, the Department of Commerce, USDA, Department of Defense (DoD), Department of Interior, Department of Justice, Department of Veterans Affairs, EPA, NASA, and NSF.

The subcommittee has prepared inventories that show how the Federal government spends its biotechnology research money, but until now it has never assessed future opportunities for biotechnology research. This year, however, the subcommittee is trying to produce a document that outlines areas in which biotechnology research might have a significant impact. The document's areas of emphasis are:

- Manufacturing/Bioprocessing;
- Environment;
- Agriculture (this working group is chaired by Drs. Young and Brady);
- Marine/Aquaculture; and
- Technology Transfer.

The agriculture working group is looking to see where Federal spending could benefit research. The goal of this effort is to

expand the knowledge base necessary to ensure and improve animal, plant, and human health and well-being within the context of environmentally sustainable systems.

Dr. Brady then directed the ABRAC's attention to the working group's December 13 draft of *Research Opportunities in Agricultural Biotechnology*.

Dr. Harlander asked how collaboration between industry and government on basic research in agricultural biotechnology would be achieved. Dr. Andow pointed out that NSF Centers receive contributions from industry, and Dr. Richard Parry noted that Cooperative Research and Development Agreements between industry and USDA's Agricultural Research Service (ARS) already are in place. Dr. Brady said that NSF had just completed its first Memorandum of Understanding (MOU) with a private foundation to fund a molecular evolution project.

Dr. Sederoff asked why the draft document did not talk about forestry. Dr. Brady assured Dr. Sederoff that the final document would cover forestry, fiber, and other disciplines related to food and agriculture.

Dr. Young pointed out that the working group's approach to the document is a new way to deal with agricultural research. He explained that USDA does not have the resources to seek out and fund all crucial fundamental research that affects agriculture. An interagency approach will enable USDA to fill this gap.

Dr. Wodzinski asked what was meant by the term "ecologically sustainable agriculture." Dr. Brady said the working group is refining its definition of that term.

Dr. Hill noted that the introduction to the draft mentions world hunger and malnutrition. If the working group is resolved to address such topics, he recommended that they be treated in a thorough, conscientious manner rather than superficially.

Dr. Young then introduced Dr. Charles Lewis, who discussed the working group's retreat of November 19, 1993, and the resulting draft document, which had been distributed as Exhibit #203 (attached as Appendix C).

**Biotechnology Working Group Retreat**

Dr. Lewis said that the retreat resulted in the emergence of several common themes that are included in the draft document. He also noted that the proposed "Infrastructure and Education" section of the document would address not only the training of

future biotechnology scientists, but also the need to add biotechnology to the curricula of public schools. Such efforts would include discussions of philosophy and values.

The participants had been asked to come up with some visionary ideas for research opportunities in agricultural biotechnology. That effort resulted in the following proposed research areas:

1. Map and sequence animal/plant/microbial genomes to elucidate gene function and regulation, and facilitate gene modification.

2. Clarify biochemical and genetic control of metabolic pathways in animals, plants, and microbes that may lead to products with novel food, pharmaceutical, and industrial uses.

3. Extend understanding of the biochemical and molecular bases of growth and development including structural biology of plants and animals.

4. Extend the molecular basis of interactions of plants, animals, and microbes with their physical and biological environment.

5. Develop gene/molecular probes and biosensors for rapid, on-site detection of chemical and biological contaminants in food, water, and the environment.

Dr. Young asked the ABRAC to review these proposed opportunity areas and to suggest some examples of how such research could be applied to agriculture. Discussion of such examples would occur at the next day's session.

Dr. Hill asked whether any thought had been giving to ranking the five areas in order of importance. He said that areas 2 and 5 appeared to focus more on applications than areas 1,3, and 4. Dr. Young said that such prioritizing had been discussed, but that the working group ultimately decided not to do so. Dr. Lauderdale suggested that areas 1,3, and 4 were basic research-oriented, and areas 2 and 5 were applied research-oriented. Another option would be to give concrete examples in each area as to how it could apply to agricultural biotechnology.

Dr. Wodzinski asked how such research would be paid for. Dr. Young explained that the working group's report would be presented to the Cabinet and to the President, all of whom would consider funding such research.

Dr. Kline recessed the ABRAC at 4:35 p.m.

Dr. Kline reconvened the meeting at 9:15 a.m., and the ABRAC continued to discuss the draft document on *Research Opportunities in Agricultural Biotechnology*.

**Research Opportunities: (Continued)**

Dr. Young urged the ABRAC members to identify research opportunities that go beyond the confines of agriculture. He noted that Federal biotechnology research is developing an interagency thrust and becoming more international in scope. For example, NIH is studying the metabolic pathways of corn. Corn is a model species that can give scientists ideas for applications to human health; at the same time, such research also benefits agriculture.

Dr. Young said that the final document must be completed by March 1, 1994. He asked that any examples developed by the ABRAC explain what information needs to be known, what the expected outcome of research might be, how such research will meet science and technology goals, and how such research will help fulfill societal needs.

Dr. Andow suggested that the second full paragraph on page 2 of the draft be rewritten as follows:

> *Aggressive Federal support for biotechnology research is essential to expand the knowledge base; to develop new agricultural markets, both domestic and global; to realize beneficial products that are safe to human health and the environment; and to exploit the potential of the technology to secure U.S. national and economic interests.*

The ABRAC agreed to the proposed revision by consensus.

Dr. Sederoff said that if this document were a research proposal, it would not succeed in generating new funding because it does not contain anything new. He suggested that to give the document a necessary element of newness and innovation, it should propose ways to solve practical problems instead of delineating broad areas of research. He suggested that the document outline specific problems in food and agriculture, and then demonstrate how research in agricultural biotechnology would help solve those problems. He also suggested that such research be conducted by multidisciplinary teams.

Dr. Lauderdale pointed out that the document was not intended to be a research proposal, and that elements of newness and innovation would be more appropriate to proposals for grants for

specific projects. Dr. Sederoff said that when he applies for money, he needs to explain why his project is new, why it is important, what the results are likely to be, and why he is the best person to do the project. The working group document does not contain any of that information, he said, and is not dramatic enough to generate any interest in granting new funds.

Dr. Wodzinski pointed out that the money allotted to basic research on a competitive basis is quite meager. For example, funding under the National Research Initiative had originally been set at $500 million; however, the actual amount of money available is only $97.5 million. He said that agriculture doesn't have enough basic knowledge to make use of biotechnology. Moreover, the multidisciplinary approach represents a real risk for young university scientists who are trying to gain tenure. Traditionally, such scientists are expected to work on their own, not in teams.

Dr. Hill suggested that one goal of the document should be to encourage universities to change how scientists are evaluated. "Going it alone" to make tenure could be a barrier to achieving research breakthroughs. Dr. Kapuscinski agreed, suggesting that incentives be given to encourage the academic system to change its ways of evaluating young scientists, and to make collaboration a plus when reviewing candidates for tenure. Dr. Letourneau said that new people in the system already are trying to encourage greater use of interdisciplinary teams in research, and that this document could boost such an approach.

Dr. Kline suggested that the ABRAC try coming up with the examples Dr. Young requested, and deal more extensively with Dr. Sederoff's concerns later.

Dr. Lauderdale suggested the enzyme phytase in animal systems as an example. He explained that when feed containing phytase-producing microbes was fed to pigs, the pigs eliminated less phosphorus. If scientists understood why this occurred, the result could be more efficient lean meat production and less phosphorus applied to land in the form of manure spread. Research in this area could provide knowledge on how to deliver enzymes to animals and on designing foods. He and Dr. Wodzinski noted that scientists in The Netherlands have cloned the phytase gene, fed the gene product to swine, and increased the swine's feed efficiency 400-fold. Dr. Young asked Dr. Wodzinski to write a paragraph elaborating on this example.

Dr. Vidaver suggested that research be conducted on combating pests of turf grasses which could be a great benefit to homeowners and golf course operators. Insects such as the white grub attack turf grasses, but biological controls have not been very effective. Fungi also attack turf grasses, but fungicides have been the only control option available and many fungicides

have been taken off the market. Applying molecular biology to these problems would lead to ways to combat insects and fungi.

Dr. Marrone suggested that research focus on control of sucking insects such as aphids and whiteflies. These insects account for a large proportion of chemical pesticides used, and they have microbial symbionts that bear further investigation. By looking at the molecular biology of the symbionts, and manipulating them to control the insects' sucking mechanisms, the insect could be prevented from destroying plants.

Dr. Witt noted that NIH Revitalization Act of 1993 requires NIH to develop a plan for using fewer animals in research. A project that would explore ways to manipulate the X and Y chromosomes in male animals' sperm so that the resulting litters would be of a single gender could help NIH achieve that goal. In addition, producers could save money and produce more with fewer animals. Dr. Young agreed, and asked Shirley Ingebritsen, Animal and Plant Health Inspection Service, to provide the statistical data needed to support this example.

Dr. Sederoff suggested that an effort be made to investigate the morphology and composition of cell walls. Basic knowledge of cell walls would give scientists the ability to change the properties of food products and wood fibers. Such changes could improve plant resistance to disease and increase the efficiency of antibiotics applied to humans and animals.

Dr. Sederoff and Dr. Kapuscinski advocated research on the genetic and molecular basis of geographic site adaptation in wild-type and modified organisms.

Dr. Marrone noted that much current research and development is limited to single-gene manipulations and she suggested focusing on engineering entire metabolic pathways for the production of useful secondary metabolites and natural products. Dr. Brady, National Science Foundation, observed that this kind of approach could result in the production of marketable, high-value products from plants.

Dr. Wodzinski suggested the importance of research on protein/carbohydrate interactions and the use of bacterial promoters for increased starch biosynthesis in corn.

Dr. Sederoff noted that many agricultural traits are governed by several genes, but the molecular basis for most quantitative traits is not known. Such knowledge, he said, could have very broad implications for agriculture.

Dr. Andow noted the current difficulties of evaluating the genetic basis of quantitative traits and of tracking organisms in the environment. Dr. Lauderdale suggested the insertion of

genetic markers into arthropods as a tracking system for gene movement. Dr. Andow further suggested monitoring gene movement based on structural genes in addition to marker genes.

Dr. Hill suggested that research focus on crops that are important to people in developing countries, such as tuber and root crops (cassava, sweet potato, etc.). Research should cover the gene function and regulation of such crops, pest resistance, and non-food uses of such crops. Such research is particularly important because the introduction to the draft focuses so heavily on world food needs. If the examples do not reflect that focus, then the introduction should be rewritten, and references to meeting world food needs should be removed. Dr. Andow expressed agreement with Dr. Hill.

Several ABRAC members suggested examples in the area of co-evolution. Dr. Sederoff stressed the importance of understanding the molecular basis of co-adaptation between host and pest organisms. Dr. Marrone noted that genetic manipulation of a plant to disrupt the chemical signals by which insects locate new host plants could be the ultimate form of plant protection. Dr. Andow emphasized the need to understand the development of pest faunas and resistance mechanisms over a time scale of centuries as well as the adaptive potential of large groups of insects.

Dr. Young asked the ABRAC members to send in any additional ideas for examples of high-impact research areas. He said the final document would be reviewed by OSTP and OMB, and would also be sent to other policymakers and those who influence them.

Dr. Kline began to discuss a report by the United Kingdom's Committee on the Ethics of Genetic Modification and Food Use.

**Report by the U.K. Committee on the Ethics of Genetic Modification and Food Use**

Dr. Kline, a primary reviewer of the report, noted that the committee focused on a small number of ethical issues related to biotechnology and food:

- The transfer of human genes to food animals;
- The transfer of genes from animals whose consumption is forbidden by certain religious groups to animals that they normally eat;
- The transfer of animal genes into food crops, which may be of particular concern to vegetarians; and
- The use of agricultural species to produce proteins of pharmaceutical importance to humans.

With respect to the transfer of human genes into food animals, Dr. Kline noted the report's finding that most people occasionally consume small amounts of human DNA, but such consumption generally does not carry any ethical implications. Moreover, when molecular copies of human genes are inserted into an animal, the inserted material is once removed from being truly human. Even so, the report acknowledges that certain religious traditions might disagree with such conclusions. For that reason, the report recommended identification (i.e. labeling) of foods that contain human gene copies so that those who object would be able to avoid such foods.

After a break for lunch, Dr. Kline introduced Mr. Stephen Burke, who updated the ABRAC on the North Carolina Conference on Food Biotechnology and Societal Concerns.

**Update on North Carolina Conference**

Mr. Burke recounted the history of the conference, and then said that about 100 people had participated in the event. The attendance and active participation of the ABRAC had been appreciated. The proceedings were completed, and had been edited only for clarity. They would be distributed through the ABRAC and the North Carolina Biotechnology Center as deemed appropriate by the ABRAC.

Mr. Burke said that he had learned four things from the conference:

1. Those who are annoyed with or say they do not favor biotechnology may actually be dealing with other equally valid issues, such as sustainable agriculture, environmental concerns, the roles of government and/or corporations, capitalism, and impatience with intractable problems.

2. The food biotechnology community often believes that biotechnology is singled out for criticism only because it is a relatively new science. Such beliefs underestimate the psychological importance food holds for most people.

3. The food biotechnology community forgets that people are less likely to be objective about an issue that is highly personal and important, such as food.

4. Society is becoming increasingly distrustful, particularly if the subject in question is highly personal or unfamiliar. This growing mistrust represents a sea change that must be acknowledged.

Several ABRAC members suggested that the proceedings be distributed more widely—through newsletters, for example—and that conference participants be interviewed on television. Mr. Burke noted that he would be duplicating some of the North Carolina conference at a Biotechnology Industry Organization conference in Toronto in May 1994.

Dr. Kline asked the ABRAC to think of other ways to follow up on the North Carolina conference, and thanked Mr. Burke for his remarks.

**Update on Biotechnology and Organic Food Standards**

Dr. Young reiterated that a discussion of organic food and biotechnology that had been placed on the agenda of the current ABRAC meeting, but that it had been withdrawn at the request of the National Organic Standards Board. The Board wanted more time to decide what issues it wants the ABRAC to consider. Dr. Young said he hoped the discussion could be rescheduled for a future ABRAC meeting.

Dr. Young asked whether sending an ABRAC representative to the Board's next meeting would be a good idea. Dr. Vidaver said that at least two members of the ABRAC should go.

Dr. Young explained that the issue for the Board is whether food derived from biotechnology could be considered organic. Dr. Sederoff noted that this question parallels those being considered in the report of the U.K. Committee on the Ethics of Genetic Modification and Food Use.

Dr. Letourneau and Dr. Kapuscinski questioned whether it would be worthwhile to participate in the Board's deliberations because the Board's way of thinking is so different from the ABRAC's. Dr. Letourneau gave the examples of nicotine and rotenone, dangerous chemicals that are allowed in organic farming because they occur naturally and are not synthesized. Dr. Vidaver questioned the interpretation of some that organic foods are safer foods.

Dr. Pierce volunteered to represent the ABRAC at the next meeting of the Board if that would be of mutual interest.

Dr. Kline then introduced Ms. Martha Steinbock, who updated the board on international activities related to biotechnology.

**International Update**

Ms. Steinbock said that the Third International Symposium on the Biosafety Results of Genetically Modified Plants and Organisms

would be held November 13-16, 1994, at the Double Tree Hotel in Monterey, CA. The meeting is sponsored jointly by USDA, University of California-Davis, the Commission of the European Community, and Japan's Society for Technological Innovation.

The first day will be spent outlining critical questions and opening them for discussion. The second day will deal with key product groups, and will include three concurrent evening workshops. The final day will employ three discussants to summarize the conference. The first announcement of the conference will be published within a month, and the proceedings will be available about two months after the conference ends.

Dr. Marrone suggested that the ABRAC hold a meeting at the same time as the conference so that members could attend it.

Dr. Pribyl, Food and Drug Administration, asked whether FDA would be a sponsor of the conference. Ms. Steinbock replied that conference organizers would welcome FDA sponsorship.

**Biotechnology Patent Issues**

Dr. Andow said that some scientists are basing their research decisions on the roles that patents are playing. Dr. Pierce said that processes, not just products, are being subjected to patenting—a development that he considers to be alarming.

Dr. Marrone said that broad patents on subject areas and processes freezes many people out of research and development. Dr. Pierce noted that not just biotechnology is affected; a patent is pending on non-standard eye surgery in the cornea.

Dr. Margriet Caswell, Economic Research Service, said that the USDA Biotechnology Council is very concerned about the potential impact of patents on research and that she chairs a working group to deal with it. She noted that in January, 1994 the Patent and Trademark Office will be holding a public hearing in California on whether there should be a research exemption when a patent is awarded. She invited members of the ABRAC to submit testimony and information for the hearing. Dr. Young invited Dr. Caswell to discuss the results of the hearing at the next ABRAC meeting.

**Future ABRAC Meetings and Other Business**

Dr. Young proposed that the next ABRAC meeting be held in the spring of 1994 and address patent issues and aquaculture research performance standards. After some discussion, the ABRAC agreed to a tentative meeting date of May 18 and 19, 1994.

Dr. Marrone asked that the meeting also include a discussion by Marjorie Hoy of the University of Florida on the potential of transgenic arthropods.

The ABRAC also agreed to meet November 16 and 17, 1994, in conjunction with the international biosafety symposium.

Dr. Kline expressed the sense of the ABRAC that the ABRAC take no action on education issues for the present.

Dr. Hill reported two developments with respect to 1890 and 1862 institutions:

1. A meeting would be held February 21, 1994, at the University of Maryland-Eastern Shore in which these institutions would work with the heads of Federal agencies on joint efforts related to biotechnology.

2. ABRAC members would be asked to participate in a meeting April 18-20, 1994 in Little Rock, AR, in which the entire 1890 community will deal with biotechnology issues.

Dr. Kline adjourned the meeting at 2:30 p.m.

Approved:

Susan McCullough

SUSAN McCULLOUGH
Rapporteur

Daniel Jones

DANIEL JONES
Editor

Alvin Young

ALVIN YOUNG
Executive Secretary

A. David Kline

A. DAVID KLINE
Chair

APPENDIX A

LIST OF VISITORS
UNITED STATES DEPARTMENT OF AGRICULTURE
AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE
Meeting of December 16-17, 1993

Jim Rasekh, Food Safety and Inspection Service, USDA
Deborah Selfridge, Selfridge and Associates, Langhorne, PA
Shirley Ingebritsen, Animal and Plant Health Inspection Service, USDA
Ann-Lichens Park, Cooperative State Research Service, USDA
Gunnar Wilhelmsen, Embassy of Norway
Robin Woo, Georgetown University
Lewis Smith, Agricultural Research Service, USDA
Ken Reid, *Food Chemical News*
David Holzman, *BioWorld*
Meryl Broussard, Cooperative State Research Service, USDA
Jay Flowers, Cooperative State Research Service, USDA
Eric Hallerman, Virginia Polytechnic and State University
Linda Murphy, American Society for Microbiology
Charlie Brown, Animal and Plant Health Inspection Service, USDA
Keith Fuglie, Economic Research Service, USDA
Althaea Langston, Animal and Plant Health Inspection Service, USDA
Karen Rogers, KKR & Company, Chicago, IL
Margriet Caswell, Economic Research Service, USDA
Cassandra Klotz, Economic Research Service, USDA
Kelly Day, Economic Research Service, USDA
Charles Urksen, Food and Drug Administration
Robert Zimbelman, American Society for Animal Science
Chris Mann, Office of Congressman Gerry Studds
Ray Dobert, National Agricultural Library, USDA
Megan Bailiff, Washington Sea Grant Programs, Seattle, WA
Oto Urban, Food Safety and Inspection Service, USDA
Pat Basu, Food Safety and Inspection Service, USDA
Richard Parry, Agricultural Research Service, USDA
Karen Cathey, Bon Vivant, Arlington, VA
Ron Buckhalt, USDA, Derwood, MD
Jim Thornton, Demeter Biotechnologies, Ltd., Potomac, MD
Richard Frahm, Cooperative State Research Service, USDA
Jim Crossan, U.S. General Accounting Office, Washington, DC
Chuck Eby, Fleishman Hillard, Washington, DC
Charles Erickson, Food and Drug Administration
Fred Stillwagen, American Cyanamid, Allentown, PA
Ian Jones, *Food and Drink Daily*
Louis Pribyl, Food and Drug Administration
Tom Brady, National Science Foundation

Revised text on aquatic performance standards from Cordle/ Kapuscinski incorporated into minutes, 1/31/94. D. Jones

United States Department of Agriculture
Office of Agricultural Biotechnology
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December 3, 1993

SUBJECT: Scope Definition for "Performance Standards for Safely Conducting Research with Genetically Modified Fish and Shellfish"; agenda item for the ABRAC Meeting, December 16, 1993

TO: Members of the Agricultural Biotechnology Research Advisory Committee (ABRAC)

Background

Each of you received the August 4, 1993 preliminary draft of "Performance Standards for Safely Conducting Research with Genetically Modified Fish and Shellfish." These draft standards were discussed at a workshop held in Minneapolis, Minnesota on August 18-20, 1993. One of the topics discussed was the "scope" of organisms for which use of the standards is appropriate.

In the August 4 draft (p.2) we defined scope as follows:

> "The performance standards address the ecological safety of research involving freshwater and marine fish, crustaceans, and molluscs, with particular emphasis on organisms expressing novel hereditary traits or hereditary traits under novel regulatory control, independent of the technology used for genetic modification."

We then provided under Section I A. (p.7-12) exit points early in the assessment where further use of the standards is not necessary for certain organisms initially included within the broad scope definition , based largely on their inability to acclimate, survive, or reproduce in the accessible environment.

Recommendations of the Workshop

Several recommendations on scope were supported by the majority of participants.

1. The scope of organisms should be based on genotype, not phenotype.

2. Exclusions should be clearly defined up front.

3. Traditional breeding resulting solely in changes in allele frequencies in the population should be excluded.

4. Interspecific hybrids which commonly occur in the accessible environment should be excluded.

Straw votes were taken on two proposed definitions:

The first definition, which was supported by about two-thirds of the participants, was proposed by Dr. Donald Campton at the University of Florida as follows:

> "An organism involving an artificially- or experimentally- induced change, rearrangement, addition, or deletion to the genomic structure of the organism.
>
> Three types of changes are included:
>
> 1. Alterations in copy number of an endogenous gene, chromosome, or chromosomal segment derived from the same taxon.
>
> 2. Artificially-induced chromosomal rearrangements (e.g., translocations, inversions).
>
> 3. Additions or substitutions of exogenous genes, chromosomes, or chromosomal segment derived from another species, subspecies, or other scientifically-recognized taxon."

The second definition, which was supported by slightly less than two-thirds of the participants, was the definition of a genetically modified organism (GMO) used in a proposed bill recently introduced into the U.S. House of Representatives concerning marine biotechnology and Federal funding. That definition is:

> "GMO means living, marine or freshwater organisms in which the genetic material has been purposefully altered at the molecular or cellular levels in a way that could not result from the natural reproductive process of that species."

After considering the various points made at the workshop on the scope issue, a proposed revision of the scope has been prepared along with a preliminary presentation of rationale for the scope definitions (see Attachment A.) The definition first broadly includes human-induced structural changes to the genome, and then provides exceptions..

Questions regarding Attachment A for the ABRAC

1. Do you agree the scope definition should be based on human-induced structural change to the genome?

2. Do the examples of structural changes clearly indicate the human-induced changes of interest? What changes, if any, would you recommend in the definition or examples and why?

3. Do you agree with the proposed exemption for interspecific hybrids?

4. Is there scientific evidence on which to base exemption of certain chromosomal-set manipulated organisms? How can we objectively provide for exemptions or guidance on the degree of sterility versus fertility occurring in different interspecific hybrids and induction of triploidy?

5. Should targeted genetic rearrangements be included in the scope? Based on science, is the rationale provided a reasonable one?

6. Are there specific questions we should ask the ABRAC Working Group on Aquatic Biotechnology and Environmental Safety to investigate further on the scope issue before revised standards are sent to the workshop participants and others for another round of comment?

Summary of Comments from the Minneapolis Workshop

Also enclosed for your information is a summary of comments from the Workshop. Dr. Anne Kapuscinski will be giving a report at the next ABRAC meeting on the Workshop and progress on assignments to revise the Performance Standards.

Maryln K. Cordle

Maryln K. Cordle
Sr. Regulatory Specialist

Attachments (2)

## Attachment A

## SCOPE

Research and Development

These voluntary standards are intended to apply to research and development conducted by the public and private sectors using the applicable organisms addressed below. While information in the standards may provide a useful starting point for evaluating the environmental safety of intentional environmental introductions in fisheries management programs or in commercial aquaculture, these activities may require additional considerations beyond those addressed in these standards for research and development.

Environmental Safety

These standards only address issues related to environmental safety, including biodiversity and genetic integrity of species. Researchers needing guidance on issues related to food safety should consult the U.S. Food and Drug Administration and published guidelines, such as the recent publication of the Organization of Economic Cooperation and Development, "Concepts and Principles Underpinning Safety Evaluations of Food Derived from Modern Biotechnology" (OECD, 1993). However, when questions of food safety are outstanding, researchers may find the guidance on confinement in Section II of these standards useful.

Applicable Organisms

A. Except as listed in B. below, the standards apply to freshwater and marine finfish, crustaceans and molluscs whose genomic structure has been deliberately modified by human intervention. Examples of deliberately induced changes in genomic structure include:

(a) additions or substitutions of genetic material[1] derived from a taxonomically distinct species or subspecies;

(b) alterations of genetic material occurring within the genome;

(c) artificially-induced rearrangements (e.g., translocations, inversions);

(d) chimeric organisms generated from fusion of embryos from taxonomically distinct species or subspecies.

B. The standards **do not** apply to organisms whose genomic structure has been modified by humans **solely** by the following means:

---

[1]Genetic material includes chromosomes, chromosomal fragments, mitochondrial DNA, genes, transposable elements, non-coding DNA (including regulatory sequences), and synthetic DNA sequences.

(a) intraspecific artificial selection/breeding by natural reproductive processes or intraspecific captive breeding, including use of artificial insemination, embryo splitting or cloning;

(b) interspecific hybridization provided that (i) the hybrid occurs naturally or has been extensively introduced (e.g., through stocking) in the environment accessible to organisms escaping from the research site or in a similar environment, and (ii) there are no indications of adverse ecological effects for the specific hybrid in question.

Genetically modified organisms included in the scope, depending upon the assessment defined in Section I, will not necessarily require precautions beyond those normally practiced in research. Some organisms, depending upon their characteristics, may be found early in the assessment (see Section I.A.) to pose little or no identifiable risk and further use of the standards for the proposed research will not be necessary. Examples include organisms that cannot acclimate and survive in the environment accessible to organisms escaping from the research site and certain sterile hybrids or sterile polyploid organisms.

Some organisms not included in the scope also may pose significant environmental risk (e.g., exotic or nuisance species whose genome has not been deliberately modified, or organisms bearing pathogens) . Guidance exists elsewhere to address these problem areas (see discussion on Regulatory Requirements below). It is not the intent of these standards to address all introductions of fish and shellfish species. Rather, the intent is to provide specific guidance regarding the effect of structural, genetic modification on environmental safety and to promote safe research with such organisms.

C. Rationale

In defining genetically modified organisms for which use of the standards is appropriate, clear objective criteria were sought that can be readily applied *a priori* to a comprehensive risk assessment such as that embodied in the standards. The objective is to include within the scope those modified organisms more likely to express novel hereditary traits or otherwise represent a new genotype for which there is very little familiarity and experience to predict environmental safety.

A novel trait may be: (1) expression of a compound not normally found in the species, e.g., antifreeze polypeptide in Atlantic salmon or the coat protein of the infectious hematopoietic necrosis (IHN) virus in Pacific salmon, or (2) a novel value in a quantitative trait, such as changes in: a metabolic rate; reproductive fertility; tolerance to a physical environmental factor; a behavior; resource or substrate use; or resistance to disease, parasitism, or predation (Kapuscinski and Hallerman 1991).

Deliberate addition, substitution, or alteration of genetic material. A novel trait resulting from expression of a compound not normally found in the is species is most likely to be produced via addition or substitution of a gene, chromosome, or chromosome segment. Gene transfer

also may give rise to mosaics in the parent generation with uncertainty about germline transmission to progeny.

A novel trait might also arise from alteration of copy number of genetic material, such as expression of an introduced copy of a gene already present in the genome of the host species (e.g., a gene for a hormone or other growth factor) if the new gene copy is under novel, cis-acting regulatory control. Therefore, not only the structural gene, but also the *regulatory elements* of the introduced genetic construct are at issue in determining whether the modified organism presents a novel trait.

The possibility of novel regulatory control of gene expression is also posed by novel pleiotropic or epistatic effects of the introduced genetic construct. The literature contains many examples of modifications where inserted DNA sequences did not act in the new host as they did in the donor organism or where alterations in one part of the genome caused surprising activity in other parts of the genome. For example, novel pleiotropies of introduced genes have been observed in genetically modified livestock (Marx 1988, Pursel et al. 1989) Novel regulation of gene expression has been linked to altered methylation of host regulatory elements (MacKenzie 1990), and is posed by trans-activation of an inactive host gene by the action of introduced genetic elements.

Artificially-induced rearrangements

Genomic rearrangements such as translocations and inversions occur randomly in nature. They involve no new genetic material; most natural mutations, although not all, are deleterious and reduce the organism's fitness.

Targeted genomic rearrangements can be accomplished through the use of recombinant DNA technology. The use of non-ionizing radiation, heat, or chemicals with subsequent targeted selection of progeny is another way of producing modified organisms exhibiting certain desired traits. Deliberately induced targeted changes, depending on the resultant phenotype, may present a higher level of risk than the random events occurring in nature. Targeted genomic rearrangements, on average, are less likely to revert to the state that existed prior to the change and their impacts on fitness are less certain, although the intent is to maintain high fitness of the modified organism in environments of its intended use. Therefore, it is considered prudent to include organisms with such targeted changes within the scope of the standards so that potential risk can be assessed on a case-by-case basis.

Ploidy manipulation

The utility of the respective types of chromosome set-manipulated organisms (e.g., triploid and tetraploid organisms) relates to improvement in desirable product characteristics and a reduction of environmental risk as a consequence of sterility. The risks they pose to natural ecosystems differ as a function of their degree of: sterility or fertility, involvement in mating behavior, and the nature and degree of phenotypic and genotypic change (Hallerman and

Kapuscinski 1993). The process of chromosomal manipulation may yield a mosaic individual in which different cells, possibly even germline cells, have different ploidy numbers. This can occur, for example, when sperm are used as a vector for gene transfer, and the resulting fertilized eggs are then manipulated experimentally to diploidize the maternal, genomic complement. This makes it hard to predict the ploidy number (and associated fertility or sterility) of descendants.

Although the sterility offered by triploids reduces environmental concerns about a modified organism, the issue of safety is complicated by three factors. First, the effectiveness of triploidy induction varies among species and the methods used. Second, although triploids are functionally sterile, the males may exhibit spawning behavior with fertile diploid females, leading to losses of entire broods and lowering of reproductive success. Third, in cases where large numbers of individuals are released, sufficient numbers of sterile triploids may survive and grow for an indeterminate number of years beyond the normal life span to pose heightened competition with diploid conspecifics or predation upon otherwise invulnerable prey (Kitchall and Hewitt, 1987). In some cases such prey may be juvenile conspecifics.

Tetraploid individuals in natural systems pose a potential risk through mating with normal diploids, yielding all triploid broods. Large numbers of such matings, resulting in large numbers of sterile individuals in the ecosystem, pose competition with and reduced reproductive success of normal diploids, increasing the risk of extinction of populations.

In spite of these potential concerns, induced sterilization through ploidy manipulation can be helpful in aquaculture systems by reducing the risk of escapees contaminating natural gene pools. Because a number of factors have to be considered in evaluating risk -- factors addressed by the standards -- ploidy manipulated organisms as a general class are included in the scope. Sterility and scale of the proposed research, as discussed in Section I.A. of the standards, may allow early exit from further use of the standards in specific cases.

Intraspecific artificial selection/breeding

Offspring of intraspecific artificial selection/breeding do not contain new alleles or additional loci and, therefore, they are not likely to exhibit novel, unfamiliar traits. Change in the allele frequency distribution at the population level is the only effect of intraspecific selection/breeding, and the extent of the trait effect is limited to the ends of a binomial distribution of allele frequencies (or penetrance of the phenotypes). Changes in allele frequency can be environmentally significant, depending on phenotype, when the change is present in the progeny at a high enough frequency and they are introduced into a small population. Such conditions are relevant in fisheries stocking programs which contemplate large numbers of releases into the environment. They also should be considered before production in commercial aquaculture systems from which selectively bred organisms might escape. However, there is far less concern in the research and development phase where large, repetitive releases are not intended or likely to occur.

Including this large category of organisms in the scope would impose an unnecessary burden of assessment on the private and public research community for a class of modified organisms which generally poses little or no risk under conditions normally practiced in research and development. Intraspecific artificial selection/breeding has been practiced for centuries, and there is no compelling reason to believe that additional guidance is needed in this area.

Interspecific hybridization

Interspecific hybridization has led to the development of new stocks for commercial aquaculture and for fisheries stocking programs. However, the release of fertile interspecific hybrids into an ecosystem containing either or both of the parental species introduces the possibility of introgressive hybridization. For example, instances of backcrossing to striped bass were observed following the stocking of white x striped bass (*Morone chrysops x M. saxatilis)* hybrids into the Savannah River system (Avise and Van den Avyle 1984). Introgressive hybridization compromises the genetic integrity of the native species, and can lead to the genetic loss of the native species, subspecies, or unique populations (Campton 1987).

A number of fertile and sterile interspecific hybrids of fish and shellfish species are produced in nature. Sterility in hybrids occurs as a consequence of combining incompatible genomes, although rarely is sterility an absolute quality rather than a quantitative or probabilistic quality. Releases of sterile hybrids can disrupt spawning of parental species' populations, and depending on phenotype, may alter competition and predation in an ecosystem with negative consequences.

Where a naturally-occurring or a stocked interspecific hybrid is extensively found in the same or similar environment as the proposed research site, and when there is no indication of adverse effects on the ecosystem for that hybrid, there should be little concern about inadvertent releases from research and development with that hybrid. Only when the research and development involves generation of unfamiliar, new genotypes or novel hereditary traits, a new hybrid with which there is little familiarity and experience, or when the hybrid is a recognized nuisance species, is it necessary and appropriate that the researcher consider the guidance provided in these standards.

**SUMMARY OF COMMENTS**
**on Draft Performance Standards**
**for Research with**
**Genetically Modified Fish and Shellfish**
**discussed at an August 18-20, 1993 Workshop**
**University of Minnesota, Minneapolis, MN**

The general consensus of participants was that this workshop was a great success. Those in attendance[1], representing a variety of backgrounds and interests, agreed that the timing and forum were appropriate for discussing issues about environmental effects of working with genetically modified fish and shellfish. Although the workshop charge was to develop performance standards for research, participants recognized that such standards are likely to contribute in the future to fostering environmental safety in commercial uses of genetically modified fish and shellfish. This underscores the importance of ending up with scientifically credible performance standards that are practicable for research and development and foster environmental safety.

Format and Timeliness of Draft Performance Standards

Participants at the workshop and interested persons who could not attend reviewed a draft (dated August 4th, 1993) of the performance standards and developed recommendations for its revision. They approved the basic format of the draft: introductory sections on scope and identification of research projects that are easily excluded from the standards; then a section on step-wise assessment of environmental effects of a proposed project; and finally a section on options for containment measures, based on the type and degree of environmental effect(s) assessed in the prior section. Other positive features noted were that the draft:

provides individuals without an ecological background an opportunity to consider ecological effects of research efforts;

recognizes a need to expand consideration of environmental impacts beyond the federally funded research community;

raises previously unconsidered issues; and

takes a pro-active approach to being socially and environmentally responsible.

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[1] If you did not attend the workshop, an agenda and a list of participants in each working group are enclosed. If you would like additional copies of these, the address list of all participants, or the draft performance standards discussed at the workshop, please contact Ms. Wendilea LeMay, Dept. of Fisheries and Wildlife, 200 Hodson Hall, University of Minnesota, St. Paul, MN 55108, ph. 612/624-3600, FAX 612/625-5299.

Content of Draft Standards

Numerous constructive suggestions were made for revision of the Standards. They all related to content rather than form. Several key concerns surfaced at the workshop and in written comments received afterwards. They are summarized below:

Scope/Applicability - The scope of the Standards and the definition of "GMO" were the subject of considerable debate. General consensus from the workshop participants and written comments was that the definition needs to relate to intentional and structural genetic changes in finfish and shellfish, with exemptions for classical selective breeding, certain common inter-specific hybrids, and certain chromosomal manipulations. The next draft will need to present a formal and inclusive definition of "GMO" incorporating these ideas.

Definitions - The need for an improved glossary is needed. It should define terms such as "negligible release/risk," "accessible ecosystem," "significant interactions," "familiarity," and others.

Subjectivity - Many of the determinations are subjective, and the standards need to be as objective as possible. All researchers should arrive at the same level of risk management for a given situation.

Incomplete Knowledge - Unfamiliarity with many organisms, environmental interactions, and a lack of appropriate models hamper the effectiveness and objectivity of the section on assessment of environmental effects.

Levels of Risk - The draft does not account for gradation between "high risk" and "no risk" extremes. The standards need to be restructured so that, at the very least, a high, medium, and low level of environmental effect are possible conclusions; these risk levels should carry through both sections of the Performance Standards. At the workshop, Group III developed the section on containment with three risk levels in mind, but questions were raised concerning whether the "high" risk containment measures were too restrictive. Also, should there should be a minimum containment protocol when working with any GMO, even if the Performance Standards indicate that it presents no risk?

Marine Environments - Marine and estuarine systems are not adequately addressed in the draft. Marine systems are open systems, and "limited release" has little meaning. A revision must address their unique features without precluding research at marine laboratories.

Shellfish - Shellfish also pose unique considerations that are not thoroughly explored. For example, should any work with a monoecious organism be considered high risk?

Biological Containment - The suggestion was made that biological containment strategies should be considered within the Risk Management section of the draft. However, questions concerning the reliability and effectiveness of using these methods as a primary barrier still need to be addressed.

Restrictiveness - A number of comments expressed concern that the Standards may be too restrictive and/or prescriptive. There was a desire on the part of all participants not to preclude research that will allow more information to be collected. Concern was also expressed that overly restrictive standards would increase costs of research.

Continuity - Cohesiveness between the two sections needs to be improved. In adopting suggestions from the three different working groups, continuity throughout the document must be achieved.

Additional concerns expressed included the possibility of the standards being co-opted for legislation, having an oversight structure to ensure compliance, and whether or not non-federally funded researchers would be expected to follow the standards.

**Future Directions**

Suggestions for additional future directions included developing a worksheet, flow charts, a set of questions with appropriate definitions as an executive summary at the beginning of the revised document, expanded appendices, and a complete glossary to make the document more useable. The suggestion was also made that development of an interactive, user-friendly, computerized, decision-support tool (expert system) would make the standards more accessible and aid in ensuring uniform application of the Performance Standards.

Other comments included the need for testing the standards with actual examples of current research, and offering workshops for researchers on how to use them once final revisions are completed. Finally, workshop participants acknowledged that more research is needed to create appropriate ecological and physiological models to better address the weaknesses in the scientific foundation of the performance standards.

**Next Step**

Progress on revisions to the draft will be presented at the next meeting of the Agricultural Biotechnology Research Advisory Committee (ABRAC), scheduled for December 16-17, 1993 in Arlington, Virginia. The meeting is open to the public. For more information, please contact the USDA's Office of Biotechnology, ph. 703/235-4419, FAX 703/235-4429. Workshop attendees and others who have indicated an interest will have an opportunity to review future drafts.

DRAFT: 12/13/93

**RESEARCH OPPORTUNITIES IN AGRICULTURAL BIOTECHNOLOGY**
**BIOTECHNOLOGY RESEARCH SUBCOMMITTEE**
**AGRICULTURE WORKING GROUP**

## I. INTRODUCTION -- THE CASE FOR FEDERAL SUPPORT OF AGRICULTURAL BIOTECHNOLOGY RESEARCH

The United States currently benefits from one of the most productive and cost-effective agricultural systems in the world. A key element among those factors contributing to U.S. pre-eminence has been the historical application of technological innovation to traditional agriculture practices. Similarly, in the global arena, the beneficial return of technology investment in agriculture is also well-documented. Technological achievement has been largely credited as the primary catalyst of the "Green Revolution" which resulted in significantly increased food production for much of the developing world during the 1960's.

Biotechnology, as an applied science with an essential foundation in basic research, offers great possibilities for improving traditional agriculture worldwide in the 21st Century. Such innovation could not come at a more timely moment. Indeed, in the face of escalating population pressures, the application of biotechnology to traditional agriculture is absolutely essential to intervene against further degradation of the earth's fragile natural resource base.

If current trends continue, the world's population will double early in the next century. And as current trends become reality, without an infusion of new technology, the real issues of burgeoning populations, decreasing food supplies, dimished agricultural productivity, and a threatened ecosystem are being brought into direct conflict with one another. Clearly, agricultural biotechnology has an important role to play in mitigating this conflict.

The United States, and its agricultural production system in particular, are poised on the threshold of this conflict ... one which has both domestic and global implications. In this scenario, one cannot divorce the U.S. national interest from the impending global crisis. The agricultural system of the United States, benefitting from the Nation's current position as a world leader in biotechnology, is thus faced with a number of unique opportunities and challenges which may ultimately impact the Nation's political, economic, and environmental interests.

The new tools of biotechnology offer a precise and cost-effective means to produce novel, diverse, value-added agricultural products which cross traditional genetic boundaries. The approach is potentially more environmentally friendly than traditional

petrochemically oriented agricultural approaches, thus offering multiple benefits to society. At the basis of this approach is a strong and vital agricultural research sector and a policy arena which efficiently supports the derivation of beneficial products from the basic research community. In this context, the mandate for Federal support to the agricultural research system becomes critical.

Along with the development of novel and useful agricultural products, comes a responsibility to ensure the product, environmental, and human safety of products of biotechnology. Effects of products of biotechnology on non-target beneficial organisms including microbes, invertebrates, and vertebrates shoulc also be assessed and monitored for short/long-term effects on ecosystem function, productivity, species abundance, and diversity. Such measures will additionally help to ensure a diversity of germplasms for ongoing and future biotechnology efforts to secure new and useful sources of genes and gene products.

**Aggressive Federal support for agricultural biotechnology research is essential to expand the knowledge base necessary to assure the health and well-being of people and agriculturally important plants and animals within the context of ecologically sustainable farming systems.** Without such support, new agricultural markets, both domestic and global, will be underdeveloped, beneficial products may never be realized, and the potential of the technology to secure U.S. national and economic interests will be under-exploited.

## II. RESEARCH OPPORTUNITIES IN AGRICULTURAL BIOTECHNOLOGY

Under each of the following areas, it is proposed that examples be used from a variety of disciplines to illustrate (a) what is not known, but ready for discovery and why it is important; (b) what can reasonably be expected from more research; (c) how the expected results of expanding the knowledge base will contribute to strategic goals; (d) how the expected results relate to identified societal needs.

1. Map and sequence animal/plant/microbial genomes to elucidate gene function and regulation, and facilitate gene modification.

2. Clarify biochemical and genetic control of metabolic pathways in animals, plants, and microbes that may lead to products with novel food, pharmaceutical, and industrial uses.

3. Extend understanding of the biochemical and molecular bases of growth and development including structural biology of plants and animals.

4. Elucidate the molecular basis of interactions of plants,

animals, and microbes with their physical and biological environment.

5. Develop gene/molecular probes and biosensors for rapid, on-site detection of chemical and biological contaminants in food, water, and the environment.

**III. INFRASTRUCTURE AND EDUCATION**

Realization of the full potential of agricultural biotechnology will require the retraining and interdisciplinary training of scientists, the educating of undergraduate and graduate students, improved school teachers training and education, improved education of students in K-12, and general public education.

**IV. PRIORITIZATION**

**V. OPPORTUNITIES FOR COLLABORATIVE RESEARCH**

**A. OTHER FEDERAL AGENCIES**

**B. ACADEMIA**

**C. PRIVATE INDUSTRY**

**VI. PHILOSOPHICAL STATEMENT ABOUT THE FUTURE, AND THE WORLD.**

**A. OUTLOOK**

**B. STARVATION AND MALNUTRITION**

**C. ECONOMY**



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